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spontaneously after 2 to 3 days. No other adverse events were observed during eltrombopag treatment or at the follow-up visits routinely performed 30 days after surgery. As eltrombopag has been associated with occurrence of cataracts in patients with immune thrombocytopenia, and MYH9-RD is a syndromic disorder predisposing to cataracts,^{2,3} ophthalmological evaluation was carried out at every follow-up visit. None of our patients showed occurrence or worsening of cataracts, not even patients 1 to 3 who already presented cataracts at baseline and received repeated eltrombopag courses.

In summary, eltrombopag successfully replaced platelet transfusions in preparation for surgery in 10 of 11 cases. Importantly, this drug provided a simple and safe option for increasing platelet count in case of refractoriness to platelet transfusions. Another advantage of eltrombopag compared to prophylactic platelet transfusions is that the drug induced a stable increase of platelet count throughout the perioperative period, thus also allowing the safe administration of a standard antithrombotic prophylaxis, and, in some cases, avoiding hospitalization. In our real-life setting, short-term eltrombopag was safe with no significant adverse events reported. However, since thrombopoietin-mimetics have been associated with potentially severe adverse events in acquired thrombocytopenias, including thrombosis, the risk-benefit ratio of eltrombopag administration should be always carefully assessed for each MYH9-RD patient. In conclusion, our data suggest that short-term eltrombopag should be considered as the first-line treatment to prepare MYH9-RD patients with severe thrombocytopenia for elective surgery.

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CONFLICT OF INTEREST

There are no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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BMI is an important determinant of VWF and FVIII levels and bleeding phenotype in patients with von Willebrand disease

To the Editor:

In the general population, it has been shown that higher body-mass index (BMI) is associated with increased von willebrand factor (VWF) and factor VIII (FVIII) levels.¹ A higher BMI is also associated with other procoagulant hemostatic changes, and may therefore protect against bleeding.¹ The

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association between BMI, VWF and FVIII levels, and bleeding phenotype is unknown in von Willebrand disease (VWD) patients. We hypothesize that higher BMI increases VWF and FVIII levels in patients with VWD, and thereby may ameliorate the bleeding phenotype. Therefore, we investigated the association between BMI, VWF and FVIII levels, and the bleeding phenotype in a large cohort of type 1 and type 2 VWD patients.

We included patients from a nationwide cross-sectional study in VWD patients in the Netherlands, known as the "Willebrand in the Netherlands Study" (WiN study).^{2,3} The inclusion criteria were hemorrhagic symptoms or a family history of VWD, and historically lowest VWF:Ag and/or VWF:RCO ≤ 0.30 IU/mL and/or FVIII levels (FVIII:C) ≤ 0.40 IU/mL (for type 2N VWD). For this study, we excluded patients with type 3 VWD (VWF levels and VWF propeptide [VWFpp] < 0.05 IU/mL), because these patients have by definition undetectable VWF levels. We categorized type 1 and type 2 VWD based on a VWF:Ab/VWF:Ag ratio of above and below 0.60.⁴

Furthermore, we excluded patients younger than 16 years old, because BMI reference ranges are different in children of a young age compared to adults. Blood samples were obtained at study inclusion. All patients signed informed consent. The assessment methods, blood sampling procedure, and laboratory measurements have been described in detail previously.^{2,3} Briefly, patients filled in a questionnaire on comorbidities, a self-administered version of the condensed Tostetto bleeding score and bleeding episodes that required hemostatic treatment in the year prior to inclusion. BMI was calculated with the formula weight (kg)/height (m) \times height (m). BMI was categorized in four groups of underweight (BMI: < 18.5 kg/m²), normal weight (18.5–25 kg/m²), overweight (25–30 kg/m²), and obesity (≥ 30 kg/m²).

We compared continuous variables between two groups using an independent *t* test, and categorical variables with a chi-square test. The association between BMI categories and occurrence of bleeding in the year prior to inclusion in the study was adjusted for confounders using logistic regression analysis. Outcomes of logistic regression analysis are reported as odds ratio and 95% confidence interval (CI). Multiple

regression analyses were used to analyze the association between BMI and VWF and FVIII levels and total bleeding score. We report linear regression outcomes as unstandardized β coefficient (difference) and 95%CI. In the logistic and multiple regression analysis, confounders were selected based on previous literature (age, sex, blood group [O vs non-O], and presence of relevant comorbidities [cancer, hypertension, diabetes, and thyroid gland dysfunction]).³ Statistical analyses were performed with SPSS Statistics version 24 (IBM Corp., Armonk, New York).

From the total WiN study population aging 16 years and older ($n = 688$), 94 patients without centrally measured VWF and FVIII levels, 14 patients with type 3 VWD and 35 patients with missing data on length or weight were excluded. We included 545 VWD patients of whom 349 patients had type 1 and 196 patients had type 2 VWD. Table 1 shows the patient characteristics. The mean BMI was 25.4 ± 4.3 kg/m². The mean age was 46 ± 15 years. There was no difference in BMI between patients with type 1 and type 2 VWD (25.5 ± 4.4 vs 25.2 ± 4.3 , $P = .550$, Table 1).

Among patients with type 1 VWD, higher BMI was associated with higher VWF:Ag, VWF:CB, VWF:Ab and FVIII:C, respectively 0.07 IU/mL (0.02–0.13), 0.07 IU/mL (0.00–0.14), 0.09 IU/mL (0.01–0.17), and 0.13 IU/mL (0.05–0.21) per 10 kg/m² increase in BMI (adjusted for age, sex, blood group, and presence of relevant comorbidities). In type 2 VWD, VWF:Ag and FVIII:C were associated with higher BMI, respectively 0.04 IU/mL (–0.02–0.10) and 0.09 IU/mL (0.00–0.17) per 10 kg/m² increase in BMI (adjusted for age, sex, blood group, and presence of relevant comorbidities). Similarly, in type 1 VWD, a linear association was observed between BMI categories (underweight, normal weight, overweight, and obesity) and VWF levels (Figure 1A), whereas in type 2 VWD, there was a linear association between BMI categories and VWF:Ag and FVIII:C (Figure 1B).

In the total VWD population, patients with normal weight had fewer bleeding episodes requiring hemostatic treatment in the year

TABLE 1 Patient characteristics

	Type 1 VWD n = 349	Type 2 VWD n = 196	Total patients n = 545
Age, mean \pm SD	46 \pm 15	46 \pm 16	46 \pm 15
Female, n (%)	244 (70%)*	109 (56%)*	353 (65%)
Blood group O, n (%)	241 (69%)*	97* (50%)*	338 (62%)
BMI, mean \pm SD	25.5 \pm 4.4	25.2 \pm 4.3	25.4 \pm 4.3
VWF:Ag	0.37 [0.23–0.53]*	0.26 [0.17–0.36]*	0.31 [0.19–0.47]
VWF:CB	0.42 [0.23–0.66]*	0.08 [0.06–0.14]*	0.26 [0.09–0.54]
VWF:Ab	0.45 [0.23–0.70]*	0.08 [0.03–0.17]*	0.25 [0.11–0.56]
FVIII:C	0.66 [0.49–0.87]*	0.38 [0.28–0.49]*	0.54 [0.36–0.77]
Bleeding score	9 [5–15]*	12 [8–17]*	11 [6–16]
Number of patients with bleeding in the year prior to inclusion per BMI category			
<18.5 kg/m ²	4/9 (44%)	1/4 (25%)	5/13 (39%)
18.5–25 kg/m ²	28/170 (17%)	41/106 (39%)	69/276 (25%)
25–30 kg/m ²	30/116 (26%)	23/59 (39%)	53/175 (30%)
≥ 30 kg/m ²	16/54 (30%)**	15/27 (56%)	31/81 (38%)**

Note: Data are presented as median [interquartile ranges], unless otherwise specified.

Abbreviations: BMI, body-mass index (kg/m²); SD, standard deviation; VWD, von Willebrand disease.

**P* value below 0.05 between patients with type 1 and type 2 VWD.

***P* value below 0.05 compared to BMI category 18.5–25 kg/m².

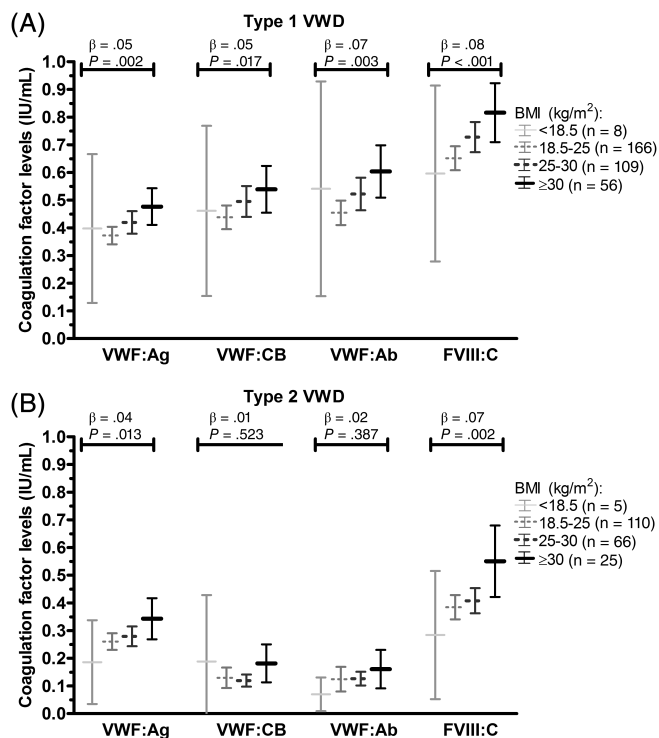


FIGURE 1 Association between BMI categories and VWF levels in type 1 and type 2 VWD. Data presented as mean and 95% confidence intervals. β outcomes of linear regression analysis. BMI, body-mass index

prior to inclusion in the study than patients with overweight and obesity, respectively 25% (69/276) vs 30% (53/175) and 38% (31/81) ($P = .018$, Table 1). In type 1 VWD, the proportion of patients with bleeding was almost two times higher in patients with obesity compared to patients with normal weight (relative risk 1.8, 30% (16/54) vs 17% (28/170), $P = .034$, Table 1). After adjustment for age, sex, blood group, and presence of relevant comorbidities, the odds ratio was 1.91 (0.89-4.11). In type 2 VWD, a higher proportion of patients with obesity tended to have a bleeding episode requiring hemostatic treatment in the year prior to inclusion than patients with normal weight (relative risk 1.4, 56% (15/27) vs 39% (41/106), $P = .113$, Table 1). In type 1 and type 2 VWD patients there was no clear association between BMI and the total (life time) bleeding score, respectively 0.54 (−1.16-2.25) and 1.35 (−0.94-3.63) per 10 kg/m² increase in BMI.

In this study we demonstrate that BMI is an important determinant of VWF and FVIII levels in patients with VWD. Although in the general population an association between BMI and VWF and FVIII levels was observed previously, this association is demonstrated in this study for the first time in patients with VWD. In accordance, it has previously been suggested that most VWF expression is seen in adipose-subcutaneous tissue, and therefore individuals with more adipose-subcutaneous tissue (ie, higher BMI) have higher VWF expression, leading to higher VWF and FVIII levels.⁵

Despite an association with higher VWF and FVIII levels, BMI does not seem to protect against bleeding. VWD patients with obesity and overweight experienced even more bleeding symptoms in the

year prior to the study than VWD patients with normal weight. This suggests that overweight and obese VWD patients, who have slightly higher VWF levels compared to VWD patients with a normal weight, are not protected against bleeding and still need to receive prophylactic treatment during interventions. Furthermore, our results indicate that the increase in VWF and FVIII levels in overweight and obese patients is insufficient to prevent bleeding, and that other determinants than VWF and FVIII levels influence the bleeding tendency of these patients⁶ more frequent surgical treatment, because overweight and obese patients may need more often surgery due to BMI associated comorbidities, such as orthopedic problems, and therefore have a higher risk of bleeding. Additionally, factors outside the hemostatic system, such as vascular damage, more frequent falls and poor wound healing could potentially have a role in the bleeding tendency of these patients.⁶ This is supported by several large studies in the past that found that obesity, despite causing procoagulant hemostatic changes, does not protect against bleeding.⁶

This is the first study to demonstrate an important association between BMI, VWF and FVIII levels, and bleeding phenotype in VWD patients. The main limitation of this study is that we did not have longitudinal VWF measurements in patients over time. However, BMI remains quite constant with aging, and therefore intra-individual analysis would probably be less informative than inter-individual analysis, which was performed in this study.

To conclude, higher BMI is associated with higher VWF and FVIII levels in patients with type 1 and type 2 VWD. However, higher BMI does not seem to protect against bleeding. Despite higher VWF and FVIII levels, VWD patients with overweight and obesity had more bleeding symptoms in the year prior to inclusion than patients with normal weight.

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CONFLICT OF INTEREST

F. Atiq received the professor Heimburger Award 2018. F.W.G. Leebeek received research support from CSL Behring and Shire/Takeda for performing the Willebrand in the Netherlands (WiN) study, and is consultant for uniQure, Novo Nordisk and Shire/Takeda, of which the fees go to the institution. J. Eikenboom received research support from CSL Behring and he has been a teacher on educational activities of Roche. K. P. M. van Galen received unrestricted research support from CSL Behring and Bayer. E.P. Mauser-Bunschoten received unrestricted research/ educational support from CSL Behring, Bayer, Baxter, Grifols, Novo Nordisk, Pfizer, Biotest, Roche and Sanquin. J.G. van der Bom has been a teacher on educational activities of Bayer. M.H. Cnossen has received unrestricted research/educational and travel funding from the following companies: Pfizer, Baxter, Bayer Schering Pharma, CSL Behring, Novo Nordisk and Novartis, and serves as a member on steering

boards of Roche and Bayer of which fees go to the institution. K. Fijnvandraat is a member of the European Hemophilia Treatment and Standardization Board sponsored by Baxter, has received unrestricted research grants from CSL Behring and Bayer, and has given lectures at educational symposiums organized by Pfizer, Bayer and Baxter. K. Meijer received research support from Bayer, Sanquin and Pfizer; speaker fees from Bayer, Sanquin, Boehringer Ingelheim, BMS and Aspen; consulting fees from Uniqure, of which all fees go to the institution. B. Laros-van Gorkom has received unrestricted educational grants from Baxter and CSL Behring. M. Coppens has received research support, lecturing and consulting fees from Bayer, CSL Behring, UniQure, Sanquin and Sanofi. All fees were received by his institution. None of the other authors has a conflict of interest to declare.

AUTHOR CONTRIBUTIONS

F.A. designed the study, performed statistical analysis, interpreted data, and wrote the manuscript. E.M.-B., J.E., K.G., K.M., J.M., M.C., M.C., B.L.G., J.B., and K.F. designed the study, interpreted data and critically revised the manuscript. F.L. conceived of and designed the study, interpreted data, and critically revised the manuscript. All authors gave their consent to the final version of the manuscript.

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Disparities in the risk of septic events in patients undergoing splenectomy for hematological malignancies (D-ROSE-PUSH): A study based on ACS-NSQIP database

To the Editor:

Studies evaluating nontraumatic splenectomy in patients with myeloid and lymphoid malignancies reported particularly higher morbidity and mortality rates, ranging between 24%-52% and 2%-18% respectively.¹⁻⁴ Infectious complications including sepsis have been reported to be significantly more common in patients with malignant indications for splenectomy.⁵ The goal of this analysis was to evaluate the risk of postoperative septic events in patients undergoing splenectomy for lymphoid and myeloid malignancies as compared to patients with nonmalignant, benign indications.

Our study was a retrospective cohort study of the prospective validated American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database from 2008 to 2016. Cases with the Current Procedural Terminology (CPT) codes 38100 and 38120 were included. These CPT codes included all the cases of total splenectomy, laparoscopic, and open that were not performed as add-on procedures. Cases with CPT codes 38101 (partial splenectomy) and 38102 (splenectomy as add-on procedure) were not included in the analysis. Only the index case was included for patients undergoing more than one procedure. Patients were not included more than once in the analysis.

The patient population was subsequently stratified based on whether the postoperative diagnosis was part of the preidentified group of "malignant lymphoid and myeloid neoplasms/leukemia." This group of diseases included the following International Classification of Disease Ninth Edition (ICD-9) diagnoses (200.X-208.X) and International Classification of Disease Tenth Edition (ICD-10) diagnoses (C81.X-C96.X). This group of diagnoses includes lymphosarcoma, Hodgkin's disease, other malignant neoplasms of lymphoid and histiocytic tissue, multiple myeloma, immunoproliferative neoplasms, lymphoid leukemia, myeloid leukemia, monocytic leukemia, and other leukemic diseases.

The primary outcome measure was the incidence of postoperative septic events, including sepsis and septic shock, at 30 days of the index

surgery in the group with lymphoid and myeloid malignancy (neoplasms or leukemia as previously defined) compared with the group without lymphoid or myeloid malignancy. Per ACS-NSQIP sepsis was considered present when a subject had evidence of systemic inflammatory response with either (i) positive blood culture (or clinical documentation of purulence or positive culture from any site for which there is documentation noting the site as the acute cause sepsis) or (ii) suspected preoperative clinical condition of infection or bowel infarction leading to the surgical procedure. Septic shock was defined as sepsis with documented organ and/or circulatory dysfunction. Both sepsis and septic shock were considered septic events. A multivariate logistic regression model for postoperative septic events at 30 days was created with adjusted odds ratios (OR_{adj}). Clinically relevant potential confounders in each separate model were considered for adjustments. Stepwise regression was performed with an entry level of 0.25 and a stay level of 0.15. The association was further evaluated across strata of age, sex, and emergency status. The interaction was assessed for the 30-day septic events outcome. All *P* values were two-sided with level of significance <0.05. Statistical analysis was done using Statistical Analysis System. In compliance with the guidelines of the American University of Beirut Institutional Review Board, ethical review was not needed for our analysis.

A total of 7721 patients met the inclusion criteria and were included in the analysis. The mean age of the patients was 54.0 years (SD 17.69 years). 52.5% of patients were female. 4081 (52.9%) of the procedures were done laparoscopically. Baseline characteristics are reported in Table S1. There was no statistically significant difference in postoperative septic events between the patients who underwent splenectomy for lymphoid malignancy vs those who underwent splenectomy for other indications without adjusting for other factors. Unadjusted risk for 30-day postoperative septic events was not statistically significantly different (OR_{unadjusted} = 1.16 with a 95% CI of 0.85-1.57) between patients with lymphoid or myeloid malignancy and patients with benign indications for splenectomy. Table 1 shows the non-stratified and stratified results on 30-day postoperative septic events across the different groups. For patients with lymphoid or myeloid malignancy undergoing splenectomy, the adjusted OR for postoperative septic events was 1.20 (95% confidence interval of 0.87-1.66) as compared to patients with other postoperative diagnoses. Based on the adjusted OR, patients with myeloid and lymphoid neoplasms were not at a higher risk of postoperative septic events. When the subgroups were stratified by age, sex, and emergency status, females undergoing splenectomy for a malignant indication were at a statistically significantly increased risk of postoperative septic events with OR_{adjusted} = 1.83 (95% confidence interval of 1.12-2.99) when compared with females undergoing splenectomy for other indications.

In our analysis, the preoperative risk factors found to be associated with postoperative septic events included older age, age 65 years or older, male sex, functional dependence, and inpatient hospitalization status. Having a higher American Society of Anesthesiologists class was associated with higher risk for postoperative septic events. The use of general anesthesia did not affect the risk of postoperative septic events. Emergency cases were associated with twofold increased risk of postoperative septic events. Perioperative transfusion, longer operative time, and open approach (vs laparoscopic) were associated with increased risk